Shiloach, Joseph 2020

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Dr. Joseph Shiloach Oral History

Director, NIH Biotechnology Core Laboratory

NIDDK

October 6, 2020

Margolin: I'm Dr. E. Gordon Margolin, volunteer in the Office of NIH History and the Stetten Museum serving today, October 6, 2020, as the moderator of an oral history of Dr. Joseph Shiloach. Dr. Shiloach is the director of the Biotechnology Core Laboratory of the NIDDK (formerly called Pilot plant). We think of Dr. Shiloach as a Biotechnologist. He will be explaining this scope of his activities during this interview which is being recorded on Zoom from our respective home and office.

Thank you, Dr. Shiloach, for your interest in preserving key NIH history and for participation in this endeavor. To start off, Dr. Shiloach, please tell us a little bit about your early life, where you were born, and a little bit about your family, and perhaps your interests as a child and how you got where you are now.

Shiloach: Okay, I was born in Israel and I had interest in biology from my early days, but in classical biology. I liked plants. I liked animals. I worked in the zoology department when I studied in the Hebrew University where I did all my studies from the bachelor to the masters, and then I did the Ph.D. in biochemistry. And then when I finished my studies in the university, I went to do my post doc in the New England Enzyme Center which was a part of Tufts University Medical School. It was a production facility which was supported, I think, by the NIH, I'm not familiar with all the details. Indeed some large-scale production of biologics which was one of the products that we were involved in at the time (which we can talk maybe later more about it) was the production of an enzyme called glucocerebrosidase from a human placenta, something that these days nobody will even think about as a source for biologics, especially for human use, and this was for a project that was supported and in collaboration with the NIH. It was done with Dr. Roscoe Brady and he had this idea of enzyme replacement therapy when you can replace enzymes that are missing, in this case in young children, with another source. These days this is a very big product that has been made in molecular biology mainly by a company called Genzyme. But anyway, I did my postdoc there and mostly developed this process. Then when I finished my postdoc studies I was offered to come to the NIH to take over at this time the unit that we call today Biotechnology Core Laboratory, but at the time it was the called Pilot Production Plant, so I came over and I took responsibility for this facility. I'm here since 1979 being in charge of this facility.

Margolin: What was your focus in your Ph.D. degree? What major were you assigned?

Shiloach: In my Ph.D. I was working on an enzyme, called the t-RNA hydrolyze. It's an enzyme that hydrolyzes the amino acid from the t-RNA. Actually, we needed to make large quantities of the t-RNA at this time and this was also my introduction into the biotechnology because we needed to grow a large amount of bacteria in order to get enough amount of t-RNA from them. And so, it was a good introduction to what we call today the Biotechnology field to develop a method of growing large amounts of microorganisms and also to do the extraction from them.

Margolin: Now you've been here at NIH ever since 1979. And you're the head now of the Core and Support Services at NIDDK.

Shiloach: It's not exactly correct because we are doing mostly core activity of the biotechnology. It's mostly the production of biologics that we are doing in this facility so it's a biotechnology core. It's not just core.

Margolin: When you say "biologicals", what do you mean by that?

Shiloach: Biologicals are all materials that are being made, that are being produced, from living live organisms, can be plant, can be animal tissue, can be bacteria, can be mammalian cells. This we call biologics as opposed to chemical compounds which are being made artificially by organic chemistry.

Margolin: So, your attempt is to isolate the biologics from the living organisms. Is that right?

Shiloach: Not only to isolate but to improve the production of these biologics and then to isolate them.

Margolin: Right—how do you know what you're going after when you attack an organism?

Shiloach: In terms of the molecule, usually you have a certain assay, a certain measurement, a certain marker that you can follow the molecule that you want or the organisms that you want. So, this is your guideline. So, when you do the production process you always follow up to confirm that this is the compound that you are looking for.

Margolin: This is something ordinarily you would say that these are hidden compounds, and somebody identifies that they're there and they want more of it. Is that it? Do you have to do the isolation first, I assume, or do you do the production first?

Shiloach: First to produce and then to do the isolation. You do the production first. You get large quantities of the organism or the plants that you need, or you buy the animal tissues. So first you get enough of this source, and then you start and do the extraction to isolate the compound that you want from this biomass that can be either animal tissues or can be plant tissues and, recently, can be bacteria or mammalian cells that these days we can grow independently. So usually you know a certain property of this compound and you try to use this property in order to fish it out—to isolate it.

But first you have large quantities of biomass and the biomass can be let's say animal tissues; if I will go back to the early days when we did the glucocerebrosidase, the enzyme needed for replacement therapy, we had a lot of tissues; so you get all these tissues and you extract them you grind them and you process them and then you get a solution that contains the soluble compound that was inside because this specific protein is soluble so you can get it out from this solution. And now you have a large amount of liquid with the protein that you want (you want some other compounds as well) and then what you do is first concentrate it because you don't want to deal with large amounts of liquid. It's always not so useful, and after that you take a certain property of this protein and you take advantage of this property and isolate the protein from the other proteins that are inside. This is a process that has different steps: you can isolate it based on size; you can isolate it based on charge; or you can isolate it based on hydrophobicity (solubilities) and so on. So you use a different type of steps in order to isolate the compound that you want.

Margolin: What are these biologics? Are they proteins? Are they hormones? Are they chemicals? What are they?

Shiloach: They are mostly proteins. Because when in your early stages you performed the crude separation you get rid of a lot of non-protein compounds easily and then you have to deal with the proteins, and then you end up with a mixture of proteins.

Margolin: I guess you want to talk about the production. I think probably what you want to tell us next is that there have been changes over the years in the methods of production.

Shiloach: The production has evolved. In the early days, most of the products, as I said earlier, were obtained from their natural sources, either from animal tissues or from plant tissues or from organisms that specifically produced this product.

So, this was in the early days when you need to get a large amount of this compound but then, with the years—so this was maybe true till about the mid-1980s, maybe late 1980s. This time the molecular biology starts to be major player and it allows you to express a certain molecule in a different organism so you don't have to take the whole organism with all kind of molecules inside just in order to get your protein, you can put a protein specifically in an organism that doesn't have similar molecules and get it out of that. So, this is the molecular biology that was introduced to specifically improve the production of certain molecules and this is the name of the game these days. And it started with these microorganisms and currently you can do it in mammalian cells very efficiently.

Margolin: How do you control the quantities that you are trying to get out, or do you just get whatever you can get? I mean do you have goals to reach.

Shiloach: Yes, usually you have goals. You need to get a certain amount to be able to do your experiment. In the early days, for example, for structural analysis you needed to have a few milligrams—you needed a relatively large amount. These days if you want to learn about the structure of the molecules you don't really need very large quantities of protein or the compound because the analytical methods are much, much better, but if you need a protein or a product for clinical use then you need to have very large amount of product and this is what all these biotechnology companies are doing and event, for example, the monoclonal antibodies just that used recently. All these are being made specific from a mammalian cells, from a culture.

Margolin: Do you get requests for these biologics from physicians or from scientists who are studying them or need them for their activities or how do you know which to go after?

Shiloach: Right, so we always worked based on what people need. I didn't try to produce any molecules. I tried to produce what people need for the research. This was the mission of the facility and this is what it is until today, so if somebody needs a large quantity of a certain compound and he can come and ask for my help. He knows where the compound is and he has a source for it and what I am trying to do, and tried to do all these years, is to come up with a better method to be able to provide him with enough of the material that they need for their research. For example, we needed a large amount of an exotoxin, which is a certain protein that was useful for a certain vaccine that we worked on, so in this case we try to improve the expression of this protein to get more protein from this bacteria. This we were able to do mainly because of the development of the molecular biology method because now we are not dealing with the native product of a producer. We have a producer that we can put anything in it and we only need to improve the production to find a better way to get more product—not only to get more product but also to find ways to purify it, to separate it from other compounds that are in the microorganism. There are so many other proteins and you need to fish only the protein that you want.

Margolin: So, you've applied the techniques to develop what the doctors or the scientists are asking for in large enough quantities for them to be able to use them and work with them.

Shiloach: Right. Correct.

Margolin: Well, that's a very important function. So you don't get on the front line. You're in the back room preparing their products for them. Is that right?

Shiloach: That's right, but this also allows us to put a lot of effort both in research and development to come up with the better method—more efficient method—for the production of all these compounds. For example, we developed a method of growing high density. It means obtaining much more bacteria in a high density culture, more bacteria or more cells in the same volume, so you can, by manipulating the media composition, by manipulating the growth condition (for example, providing them with oxygen or maybe sometimes replacing the media), so you can multiply the amount of microorganisms and get much larger quantities of the product. For example, one of the proteins that we produced was endostatin that was needed for some cancer research.

Margolin: What is that protein?

Shiloach: Endostatin. This was actually work that was done together with the Harvard Medical School with Dr. [Judah] Folkman at a time and they needed large amounts of this product and it was made in a fungus, not really in bacteria. It's called Pichia Pastoris. It's a good source of a good organism for production of a lot of biologics.

So, this project drove us to try and improve the gross production of this Pichia and to find out ways to get large amounts of protein from large amounts of cells and then large amounts of protein from this organism. So, this is just a small example, but we did it quite often after that. After the product [we provide] seems to be what the research needs, then we try to come up with a better or more efficient production procedure.

Margolin: Is it all trial and error or are there specific rules you follow to move through the process?

Shiloach: It's both. It is trial and error, but it's based on what we know about the metabolism of this organism, what it needed for its growth and what affects their production. For example, the Pichia Pastoris that I mentioned, their carbon source—it grows on methanol like, you know, E. coli grows on carbohydrate mainly, but Pichia grows on methanol.

So, you know, the methanol is the carbon source and you can play with the strategy of adding methanol to the culture and so it's specifically for this organism and different methanol addition strategies allow us to get more biomass. If you get more biomass, I mean more producer, you are also supposed to get more product.

Margolin: And you must deal with lots of different organisms and plants, how many do you use?

Shiloach: Correct. That's a very good question. In the early days we dealt with, I don't know, a hundred, if not hundreds, maybe close to 100, different types of organisms to produce the product from them because at this time molecular biology was not really developed. So, you have to get product from a single organism. These days there are different producers. We have many bacteria like E. coli that you can produce protein from them by molecular biology method. This is the recombinant technique—you put in the E. coli something that it doesn't have naturally but now produce it specifically. Then you also go into the Pichia pastoris that I mentioned as another example. Maybe in the last 20-25 years the mammalian cells became the big source of protein production and this is actually the main source of protein being produced these days for clinical use.

Margolin: You call these engineered cells or engineered bacteria that you actually make so that's a different thing that will produce more of what you're trying to get out.

Shiloach: Right, but you see they engineered the bacteria or the mammalian cells. This is the role of the molecular biologist and I'm not a classical molecular biologist. I get the organism with the specific capability of producing a special product, now I go in and try to improve the production of this protein from these organisms. So, the molecular biology is being done by the molecular biologists. They engineered the cells; they engineered the bacteria; and we actually do the production, obtaining the product from it.

Margolin: If I wanted you to produce something for me and I gave you the background including the engineered cells, how long would it take me to get a sufficient amount of material made by you? How long does it take you to do one of these processes?

Shiloach: So, it depends if it is there and the researcher can show that he gets some production. I can do a small-scale experiment and give him the product. This can take—it depends if it is bacteria—it might take a few days. If it's mammalian cells, it might take a little bit longer. Then what he does, he tests and if the product is right and this is what he wants. Because, one important thing is that when you move the production from the petri dish or from the small flask that you use in the lab into a production vessel you may change the properties of the product or maybe you change the properties of the expression so it can affect the quality. So, if the product is the same and he's satisfied with it then we can do it.

Margolin: What do you call a large production?

Shiloach: That's a very nice question. When I came, we did production in thousand liters. We have 1000 liters bioreactor that we grew bacteria in it.

Margolin: Wait a minute. I didn't get that—a thousand liters! Say that again.

Shiloach: It was in liters, yes, thousand-liter vessel that we grew bacteria we needed.

Margolin: That's pretty big.

Shiloach: Okay, pretty big. This were the early days and this is early and it's a nice question that you asked because for nowadays you also use thousand liters but it's a different approach, but because there was no way to increase the product formation per organism so you needed to do large quantities. But then with the years two things happened. First of all, the analytical methods were improved so people don't need a very large quantity of product. Secondly, with the molecular biology the production per bacteria was improved so these days I'm not running the 1000 liter; I have a 50-liter bioreactor and a 100-liter bioreactor and that's enough for what is needed for research purposes.

Margolin: The quantities you get from any one organism must be very tiny, so you really need big vessels to collect the products.

Shiloach: Correct, this was in the early days but as I mentioned before, today with all this molecular biology technique you can improve production of specific molecules from an organism by manipulating it genetically; you don't need large quantities. You can increase the production from a certain organism maybe 1000 times by using these procedures.

Margolin: And you can increase a particular biologic within an organism before you do the production.

Shiloach: Right again. This is not what I'm doing. This is what the molecular biologist does, that I'm working with, that's what he does. He engineered bacteria and put his product in it. He makes sure that he gets enough product, but he can grow only small quantities in his lab and it's not enough. So, then he comes to us and we do it on a large volume.

Margolin: I see, and I assume over the years there has been continuous improvement in your ability to increase the quantities in a favorable way.

Shiloach: Right. Also we developed a method for increasing the amount of organism per unit volume. For example, when a scientist does it in his lab in the shake flask, he may get, let's say, one gram per liter of bacteria—but maybe this is also exaggeration, maybe one gram. But we can do it and we can get maybe 100 gram per liter, 10 times higher, by growing it under more careful conditions and controlling the environment more carefully so the efficiency is higher.

Margolin: Well, that's very exciting that you've made all those changes in technology over time. Looking through your biography, I see you've dealt with all kinds of different organisms and all kinds of different materials that you've extracted. Tell me some examples of things that have been very effective that have been applied scientifically by the scientists that have been useful clinically.

Shiloach: That we did from products that we produced?

Margolin: I didn't get what you said.

Shiloach: You mean you want an example of specific products that we improved expression.

Margolin: Yes, and then how they've been applied clinically or if they have been useful to the scientists.

Shiloach: Okay. So, one example that I mentioned to you before this was the glucocerebrosidase that was done very early. Later on, we worked with the malaria vaccine production unit of the NIAID and we helped them in getting higher production of the protein that they needed. Actually, later on, they created their own production facility because they needed much larger quantities. When they needed also a different product that we were not able to supply, they implemented most of the methods that we had developed. They came with their own method as well, so they are producing it independently there. So that's is another example. We produce a lot of a polysaccharide from organisms that we needed for a shigella vaccine and salmonella vaccine. This was someone else's vaccine work that was done with the NICHD, with Dr Schneerson and Dr. Robbins. This was a major work--not only the polysaccharide but also the carrier protein that was attached to this polysaccharide for the conjugated vaccine project.

Margolin: And have you developed a lot of vaccines as a result?

Shiloach: Well, they came up with several vaccines that were actually licensed. This was a major product we made. Also, we worked with them together on the Bortedela pertussis vaccine, the whooping cough vaccine. This was a major range of project and the work that we did with the NICHD on the conjugated vaccine initiative.

Margolin: So, they come to you for those specifics and you certainly are very helpful. Very good.

Shiloach: This was good because it was not only the service. I mean we worked together; it was a collaboration. That's what I tried to do all these years. We are classified as a service, but we are not really charging the people for their work. This is part of the research activity of the NIDDK which I find very unique and very efficient, so we are not charging anybody for the work. We are working together on certain projects.

Margolin: Over the years with the increased knowledge of the biologics that are being developed, have there been more and more changes, for example, since the genome has been described, does that change your approach to some of the things you do?

Shiloach: Yes, definitely. It's changed a lot in that, especially in the recent years. What we are doing, since my goal is to try and get better production, improved production. If we know more about the organism, we can really find better ways to improve the production from the organism by changing all the metabolism, by changing some of its genome, or identifying genes for a specific association with expression of this protein. Especially we did it a lot with E. coli and recently, and this is something that I didn't mention or maybe very shortly, in the recent days in the current period most of the productions are being done from mammalian cells. So, in this case we try to identify specific genes or specific molecules in the mammalian cells that if we modify them, we can increase the expression of the recombinant protein produced from them.

Margolin: What's your source of mammalian cells?

Shiloach: Mammalian cells that we are using are mainly two types: they are the CHO cells—that's is Chinese hamster ovary cells—and also the HEK cell.

Margolin: Where do you get them from?

Shiloach: There are cells that are in the depositories so you can buy, or you can get them from depositories.

Margolin: So, you can deal with specific cells that have already been pre-selected for you.

Shiloach: Right, the cells are selected but the cells are like the bacteria; you can get the bacteria and, the person who would like to get expression takes these cells and he puts his protein inside his gene that he wants to express and then he gets expression. What we try to do is to improve the expression and also to try and improve the processing to do the recovery of the protein from these organisms more efficiently.

Margolin: There are a lot of strands in the genomes that are unknown as to what their function is—are you finding functions in some of these unknowns in terms of producing more of these products?

Shiloach: We did some. We are doing some work on identifying specific genes that may improve expression of the recombinant protein from these cells. That's what we can do but I'm not trying to find a new function for production.

Margolin: I still don't have a good picture of the clinical applications for all your products. Is there publication of all of these products that you turn over to the scientists and some of the outcomes that have been useful in the medical world. Are we getting findings that are applicable to everyday medicine?

Shiloach: The scientists have their mission for their products, and they get an effect, they do it all the time. Mammalian cells these days are made to produce recombinant proteins. Maybe I'll back up a little bit and just mention that from the beginning, in the first stage when I came in, was production from native organisms. Then in a few years came the introduction of molecular biology in creating of recombinant bacteria that produce specific proteins that the research wanted. Then the third phase was the introduction of production from mammalian cells that are being treated very similar to bacteria that are being engineered to produce a specific product. The advantage of mammalian cells is that the product that comes from them is actually more suitable for human use than the product that comes from bacteria. Results with bacterial products nowadays are mainly used for maybe structural studies, for understanding the molecule structure, but the therapeutics are coming from the mammalian cells. This is the current status, so we actually spent time and came up with new methods of dealing with processing these mammalian cells. This was one of our really main achievements that we did: It was the elimination from centrifuging the cells, as is done with bacteria, to separate the cells and fluid after the growth in the big bioreactor. Here we introduced a process to separate the cells from the liquid by using Hollowfiber, which is a very thin tubing of filters, that you pass the cell suspension through them and then the media goes out with the product that you want. So you can separate the cells which contain most of the protein that you don't need, and then you have a supernatant or clear solution that you can separate the product that you need from that and it's much easier.

Margolin: It sounds like very tedious work to me, involving the details that only people like you can do. There must be a lot of different isolatable biologics in each of these organisms that you deal with. How do you get just one of them out, that is, isolate the one you want?

Shiloach: Right, I think it is very exciting because it allows us, especially the environment here, it allows us to come up with the new methodologies that use to improve the process, some of the methodologies were adopted worldwide. I mean I am not the only one, but I think we did very early—like this the one that I mentioned to you about the filtration technique of separating the cells. Previously, we developed what we call an expanded methodology to separate the product from the cells and because when you grow bacteria and the product is in the supernatant, you need to separate the cells first in order to purify it and we incorporated a method that implemented together the separation of the cells and also the collection of the product. So, this actually later-on was popular for a while as it was called expanded-bad technology, but later on it was not very useful mainly because of some issues of contamination and it was not really adopted. But it was a very exciting process, a project for improvement.

Margolin: You also supplied me with some pictures of the equipment that has changed over the period of time. Tell us a little bit about what the newer equipment does that the old didn't do.

Shiloach: Right, so in the early days the growth of the organisms was done in a big vat. It was not very efficient mixing and there was very limited in what could be done on the control in the vessel. And later on, with the years, the vessel was developed so that the deficiency of the vessel was improved a lot because the vessel mainly keeps the bacteria or the mammalian cells sterile inside. But it also supplies them with oxygen if they need it and controls the growth condition, the temperature, and the pH, and the oxygen level. So, this was improved a lot with the years.

And we also had a very big role in developing a method called high density bacterial growth that can improve the amount of microorganisms in the vessel 10 or even a hundred fold by improving the aeration and the mixing and the way to supply the media into the culture. So, you know, now you can get higher concentration of cells or many bacteria in the same vessel by controlling the aeration better so the vessels are much smaller. That's one of the things that I mentioned earlier that when I started I have a thousand liter and nowadays I can do what I did in thousand liters when I came, in 50 liters or maybe 100 liters so you don't really need a very large vessel.

Margolin: What are the vessels made of? Are they glass?

Shiloach: Okay, the vessel originally was made from glass and small one, but then later on they were made from stainless steel. Then in these days when the production is done from a mammalian cells, the production is mainly done in big plastic bags—the stainless is only to hold the plastic bag inside. So, the plastic bag comes up already ready, but this can be done only for mammalian cells. You cannot grow bacteria in these plastic bags very efficiently.

Margolin: Do you find a lot of the same common biologics in bacteria as in mammalian cells?

Shiloach: Not really, especially these days. What was being done, you engineered the organisms to produce the product that you want.

Margolin: I see

Shiloach: So, it's being done by engineering the mammalian cells which are much more flexible because they have a lot of mechanisms that bacteria don't have. Since the proteins that are needed these days are human proteins, it's better to produce them in mammalian cells than in bacteria. It doesn't mean that you don't produce a lot of protein in bacteria but not as much, I think. I 'm not sure.

Margolin: That makes me think of the rejection phenomenon occurring because transplanted cells are incompatible with the new host. Do you have incompatibility in the cellular material you produce in terms of using it in other human beings?

Shiloach: No, because in this case it's the product that is being used; it's purified so it's only the specific product that's been needed for the treatment.

Margolin: So, there's no rejection phenomenon issue at all because you're not dealing with foreign tissue. You are only dealing with a pure protein. Your offerings can be used much more widely than tissue protein transplantations can be used. I mean they're really a transplantation in a sense, isn't it? I didn't understand if you put in selected proteins, let's say into vaccines, they don't get rejected because they can be used in anybody. On the other hand, if you transplant a kidney in somebody it has to be a tissue match.

Shiloach: Right. Correct. Yeah, because here you're dealing with this pure purified product, not intact tissue.

Margolin: You have a lot to offer that's really great for clinical application.

Shiloach: But these days I have to admit NIH grew up. It's a very big institute and there are similar facilities to ours that are more specific. For example, the NIAID has its own facility, I think, which is very modern and very big and they do all this work independently also produce material that can be used in humans for human use so something that we cannot offer.

Margolin: Do you supply products mainly for NIDDK?

Shiloach: We supply stuff in this these days for many, for NIDDK, for NIAID, and also for the FDA, for NICHD, for NCI mainly for structural study.

Margolin: You said before that for the most part the scientists know what they're looking for and they ask you to elaborate the material and produce more for them. You don't just go hunting and pecking around and finding stuff that maybe it has use and maybe it doesn't. Is that right?

Shiloach: That's right, but I'm not looking for them. What I'm looking for is a better method and better ways of producing the product and better ways of a recovery of the product. There are steps that are called upstream and downstream. The upstream is growing the organisms, getting the biomass. The downstream is the process of the recovery and then of collecting the molecules from them. I'm dealing mostly with this part of the production and with the downstream.

Margolin: Your job is really in production. It's very skillful and a lot of work.

Shiloach: Right. In production and also, as I said, these days I'm putting a lot of effort in trying to improve the production from the organism, to find out how we can get more product from certain cells or certain bacteria to understand better. And this we can do these days because of development of the genome information and all the genes that are in the bacteria or in mammalian cells you can identify specific genes. You can identify how they behave during production process or during the growth and maybe try to modify the organism or the cells.

Margolin: So, tell me now that you've been here since 1979 at the NIH, what have you seen that's changed or different about NIH now from when you first came.

Shiloach: Change? It changed a lot. I mean that's true. I think it's more improved, I would say it got much bigger and I think it's more compartmentalized. For example, there are now more production process facilities in NIH, such as at the Vaccine Research Center as well as in NIAID and in probably other research centers here. There is not much need for large quantities because you can do a lot of work with a very small amount of material, something that was not possible in the early days. Also, another thing is that most of the products that are being needed these days for research have to be suitable for human use, so this requires a lot of a cleaning methodology that we call GMP—good manufacturing practices. Which, we cannot offer because this is a completely different responsibility. So that's what I think is the major thing. I think a lot of a lot of things are being done also outside the campus, not here on the campus.

Margolin: Well, you have both the internal and the external programs so there must be a lot of people in the country doing this kind of work now. Right? Do they come to you for guidance?

Shiloach: They come in sometimes and ask me questions about instrumentation that they would like to use and if I can help them with choosing equipment.

Margolin: Okay. It's just intriguing to me what you do. I just can't get over the ability to remove certain biologics and isolate them and apply them. To me that's a wild world you live in but with very specific applications which are overwhelming to me and probably very useful in the world at large. I think this interview has highlighted remarkable accomplishments and offerings, along with all the progress you have added over the years.

Do you have anything you want to add that we may have skipped over that you'd like to emphasize or tell more about? Things you have thought about that you want your successors to know about your work?

Shiloach: I just would like to say that it was a very good journey, a long trip from the very beginning of getting product just from tissues or organisms that existed and then to move on into the molecular biology field when you can get the products made from recombinant organisms and then you can get them from the mammalian cells rather than processing large amount of tissues as we did in the early days. If I will tell somebody that we used to grind 100 kilogram of bull testicles to produce calmodulin which was a very attractive molecules for researchers at the NIH at the time. Now you can do it in a small vessel and get almost the same results. So, this this was really a good journey. Also, all the development in the process with the getting better methods of production and expression and secretion or open processing and later on better and better methods of improving the expression from the organisms by manipulating them genetically. So, I think it was a very fascinating journey for me.

Margolin: You have no regrets over these years you've spent here at NIH.

Shiloach: I think it was very nice—I mean development process—very nice journey for me and the staff—and I am very grateful that I always had a very good support and I worked with a lot of people in all these institutes around, especially until about 10 years ago before this new southern facilities came up. I really never had any issues; it was a pleasure to work with the people. I think the creation of the facility that was part of the research is especially important. The services are the major merit of this, obviously, because you can do production, but you can also do development and research and you are not constrained by getting just product. You can also get better process.

Margolin: Oh, it's so nice you've been here this many years and you're still excited about it. That's very enthusiastic.

Shiloach: I talked to you and I had a chance to think about all this time that has passed. I mean, I think, I was really lucky and grateful for that.

Margolin: Well that's very good. You don’t have any other questions and you apparently have covered pretty much what you wanted to tell us about. Is that right?

Shiloach: Yes, I think so. I think that I did mention every little thing but I wanted especially to emphasize that the journey through implementing all the development in the science, improving the production capabilities, and upgrading all the instrumentation and also the approaches and then the processes, and then came the molecular biology techniques. It all leads to, I think, the biotechnology industry that we have today.

Margolin: What you've given us is a great; it's a great, as you say, journey that really fits into the desire of fulfilling our function at the NIH Office of History—the expectation that we've been able to capture all this and keep it current so people who want to know the history of your projects and development will have these items immediately available. I feel this has been great as this discussion highlighted a great deal of interesting and important historical information.